SYNTHESIS, CHARACTERISATION AND BIOLOGICAL STUDIES OF SOME NOVEL BIOACTIVE HETEROCYCLES

Final synopsis

OF THE Ph.D. THESIS TO BE SUBMITTED TO THE MANGALORE UNIVERSITY

FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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SYNOPSIS

CHAPTER-1

A BRIEF REVIEW ON CHEMISTRY OF PYRAZOLE AND TRIAZOLES

Heterocyclic compounds are cyclic compounds with the ring containing carbon and atleast one other hetero elements such as oxygen, nitrogen, sulphur , etc.. The simplest of the five-membered heterocyclic compounds are pyrrole, furan and thiophene. Similarly five membered rings containing more than one or two heteroatoms are as pyrazole, thiazole, triazole, thiadiazole, oxadiazole, imidazole, purines etc..

The chemistry of heterocyclic compounds has become an interesting field in the investigation of bioactive molecules from long time. Hence the chemistry of heterocyclic compounds have gained immense importance in human life because of the variety of applications. They play a pivotal role in the metabolism of living cells. Nitrogen, oxygen and sulphur containing heterocyclic compounds are key building blocks used to develop compounds having biological/medicinal application.

Among them, nitrogen containing heterocycles have received special attention in pharmaceutical chemistry due to their diverse medicinal potentials. Heterocycles with one heteroatom are generally stable where as heterocycles with three atoms in the ring are more reactive because of the ring strain.

Heterocyclic compounds play an important role in developing new antimicrobial agents with new mechanism of action. These heterocyclic compounds are well known to possess diverse pharmaceutical properties[1]. They are found in various natural products and have been identified as products of chemical and biological importance , the synthesis of nitrogen heterocycles has also attracted wide spread attention owing to the diverse application in agricultural , industrial , food , flavorings , dyes , rubber , chemical and adhesive sectors[2].

Pyrazole and Triazole are well established in the literature as important biologically active heterocyclic compounds. These derivatives are the subject of many research studies due

to their widespread potential biological activites like anti-inflammatory[3], antibacterial[4-5] , anticancer[6-7] , anti-convulsant[8], antidepressant[9] , antiproliferative[10] and antoxidant[11-13] activity .Furthermore pyrazoles having selective inhibitors of cyclooxygenase[14] , antidiabetic[15] and non nucleotide HIV-I reverse transcriptase inhibitory activities[16] were reported .

Keeping in view of these observations, a project has been undertaken to synthesize heterocyclic derivatives containing pyrazole and triazole moiety, with a view to evaluate their biological activities and to develop some alternative methods for their synthesis. The results of such studies form the subject matter of this thesis.

CHAPTER-2

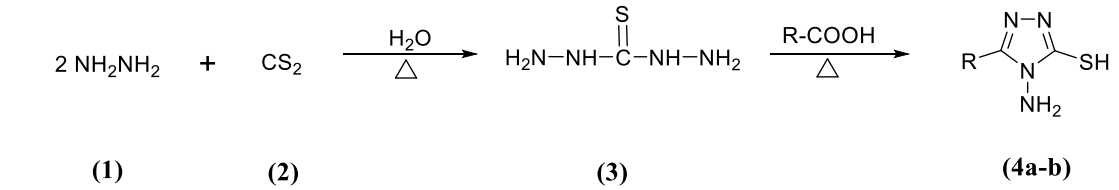
SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL, STUDY OF PYRAZOLE CARRYING 3-SUBSTITUTED-[1,2,4]TRIAZOLO [3,4-B] [1,3,4] THIADIAZOLES

Synthesis of 3-substituted-6-(3-methyl-1-phenyl-5-(aryloxy)-1H-pyrazol-4-yl)-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazole **(15a-l)** is depicted schematically in **(scheme 2.3).** To begin, Condensation of thiocarbohydrazide **(3)** with acetic/n-butyric acid, gave yield a 3-alkyl-4-amino-5-mercapto-1,2,4-triazole[17,18], **(4a-b)** while 3-phenyl-4-amino-5-mercapto-1,2,4-triazole[19,20] **(8c)** was synthesised by reacting ethyl benzoate with hydrazine hydrate and then adding carbon disulphide in ethanolic potassium hydroxide. The resulting potassium dithiocarbazinate was treated with hydrazine hydrate to get 3-phenyl-4-amino-5-mercapto-1,2,4-triazole **(Scheme 2.1).**

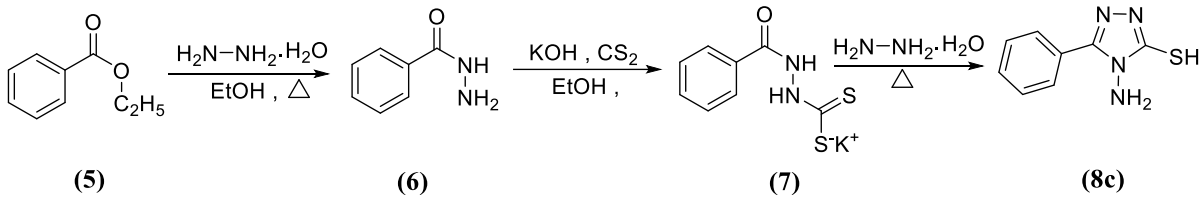
Redistilled ethyl acetoacetate **(10)** produced 3-methyl -1-phenyl -1H-pyrazole-5-one **(11)** when treated with phenyl hydrazine **(9).** After Vilsmeier-haack formylation, it yielded 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde **(12).** It was then dissolved in dimethyl sulfoxide and reacted with substituted phenol, in the presence of catalytic quantity of potassium hydroxide to gave 5-aryloxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde[20,21] **(13a-d).** These aldehyde undergo oxidation when treated with potassium permanganate in aqueous ethanol to yield 5-aryloxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid[22] **(14a-d) (Scheme 2.2).**

The final products, [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives carrying substituted aryloxy pyrazole, were obtained by condensing 3-alkyl/phenyl-4-amino-5-mercapto-1,2,4-triazole with 5-aryloxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid in the presence of phosphorus oxychloride[23]. **(Scheme 2.3).**

Structure of all newly synthesized compounds were supported by analytical and spectral data. The new compounds were also screened for their antimicrobial[24,25] and antioxidant[26] activities.

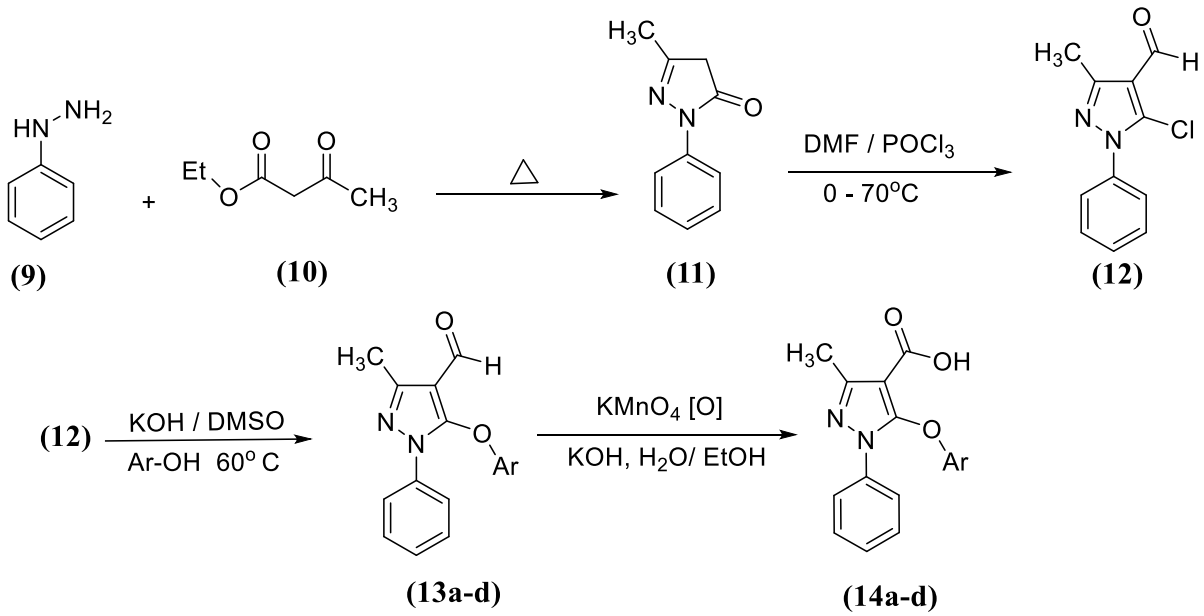


(1) **(2)** **(3)** **(4a-b)**



(5) **(6)** **(7)** **(8c)**

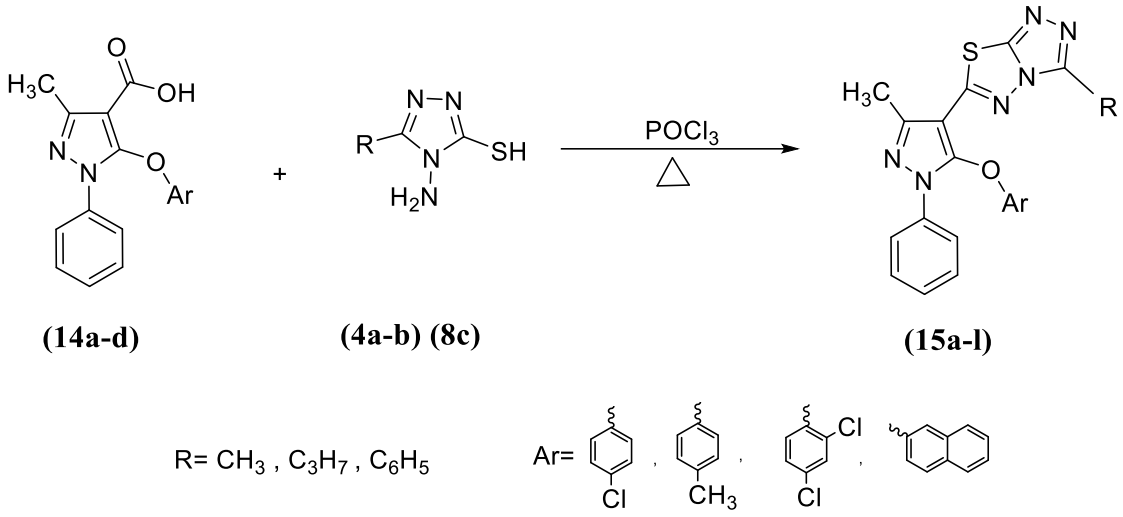
(scheme 2.1)



(9) **(10)** **(11)** **(12)**

(13a-d) **(14a-d)**

Scheme (2.2)



Scheme (2.3)

CHAPTER-3

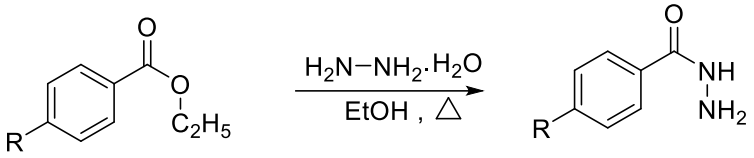
SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL STUDY OF PYRAZOLE CARRYING SOME NOVEL 1,3,4-OXADIAZOLES

The synthesis of hitherto unreported title compounds namely 2-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-(4-substituted-phenyl)-1,3,4-oxadiazole **(18a-p)** are as outlined in **(Scheme 3.2).** The substituted hydrazide **(17a-d)** was synthesized by reacting different substituted ethyl benzoate **(16a-d)** with hydrazine hydrate[27,28] **(scheme 3.1).**

The synthetic route followed for the preparation of 5-aryloxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid **(14a-d)** by the respective aryloxy pyrazole aldehyde **(13a-d)** is outlined in **chapter 2.**

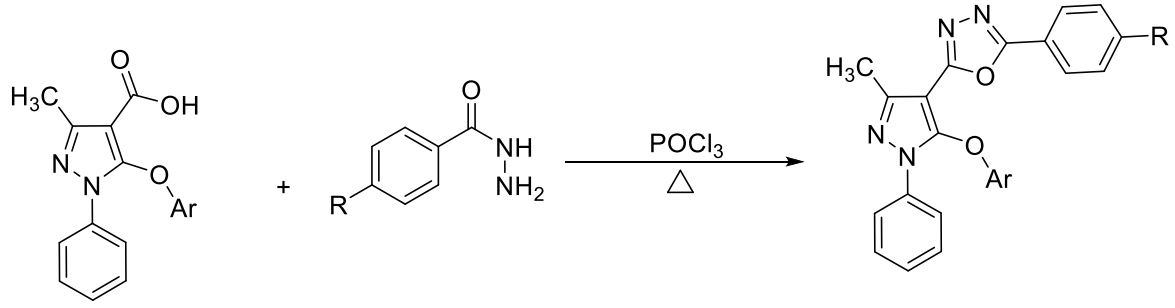
The final products, 1,3,4- oxadiazole derivatives carrying substituted aryloxy pyrazole were obtained by condensing 5-aryloxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid **(14a-d)** and substituted hydrazide **(17a-d)** in the presence of phosphorus oxychloride[29] **(scheme 3.2).**

Structure of all newly synthesized compounds were supported by analytical and spectral data. The new compounds were also screened for their antioxidant and antimicrobial activities.



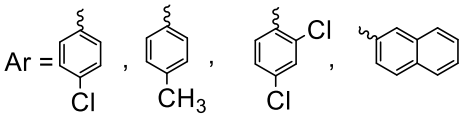
(16a-d) **(17a-d)**

(Scheme 3.1)



(14a-d) **(17a-d)** **(18a-p)**

R= H , OCH_3, NO_2 , Br

Ar = 

(scheme 3.2)

CHAPTER-4

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDY OF 4-((*p*-SUBTITUTED BENZYLIDENE)AMINO)-5-SUBSTITUTED-4H-1,2,4-TRIAZOLE-3-THIOL

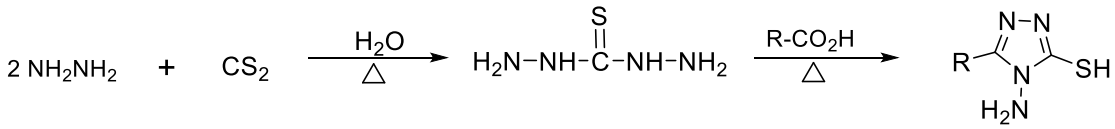
The schematic route for the synthesis of 4-((4-subtituted benzylidene)amino)-5-substituted-4H-1,2,4-triazole-3-thiol tautomerism of 4-((4-subtituted benzylidene)amino)-5-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thione **(26a-l)** is as shown in **(Scheme 4.3).** Thiocarbohydrazide **(21),** the starting compound, has been produced by combining carbon disulfide **(20)** with hydrazine hydrate **(19).** It was then refluxed with a number of derivatives of carboxylic acids (acetic, propionic and n-butyric acids) to produce 3-alkyl-4-amino-5-mercapto-1,2,4-triazole **(22a-c),** for the general procedure followed by same as the preparation of compound **(4a-b)** explained in the **chapter 2 .**

The synthetic route followed for the synthesis of 3-phenyl-4-amino-5-mercapto-1,2,4-triazole **(8c)** by the respective potassium dithiocarbazinate **(7)** is outlined in **chapter 2 .**

p-Fluorobenzaldehyde **(23)** and secondary amine **(24a–c)** (pyrrolidine, piperidine, morpholine) reacted with the presence of potassium carbonate as a base and N,N-Dimethylformamide as a solvent to produce secondary amine substituted benzaldehyde **(25a–c).**

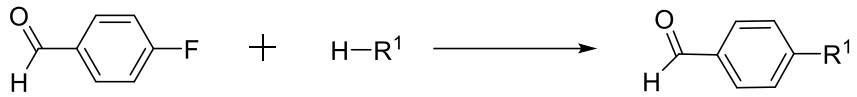
The final products, schiff base derivatives carrying secondary amines were obtained by the condensation of 3-alkyl/phenyl-4-amino-5-mercapto-1,2,4-triazole **(22a-c) (8c)** with secondary amine substituted benzaldehyde **(25a–c)** in the presence of catalytic amount acetic acid and ethanol as the solvent[30]. **(Scheme 4. 3)**

Structure of all newly synthesized compounds were supported by analytical and spectral data. The new compounds were also screened for their antioxidant and antimicrobial activities.



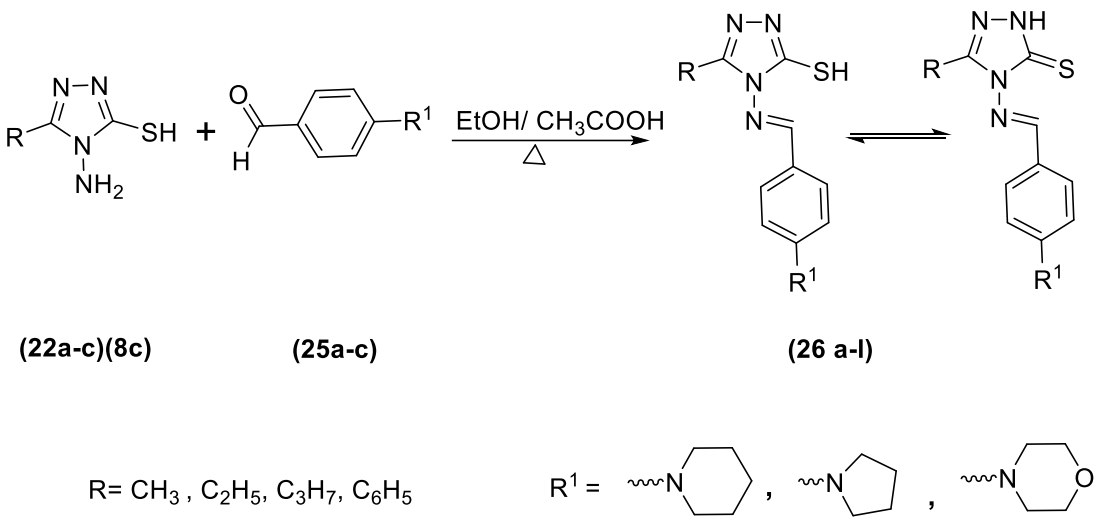
(19) **(20)** **(21)** **(22a-c)**

(scheme 4.1)



(23) **(24a-c)** **(25a-c)**

(Scheme 4.2)



(Scheme 4.3)

CHAPTER-5

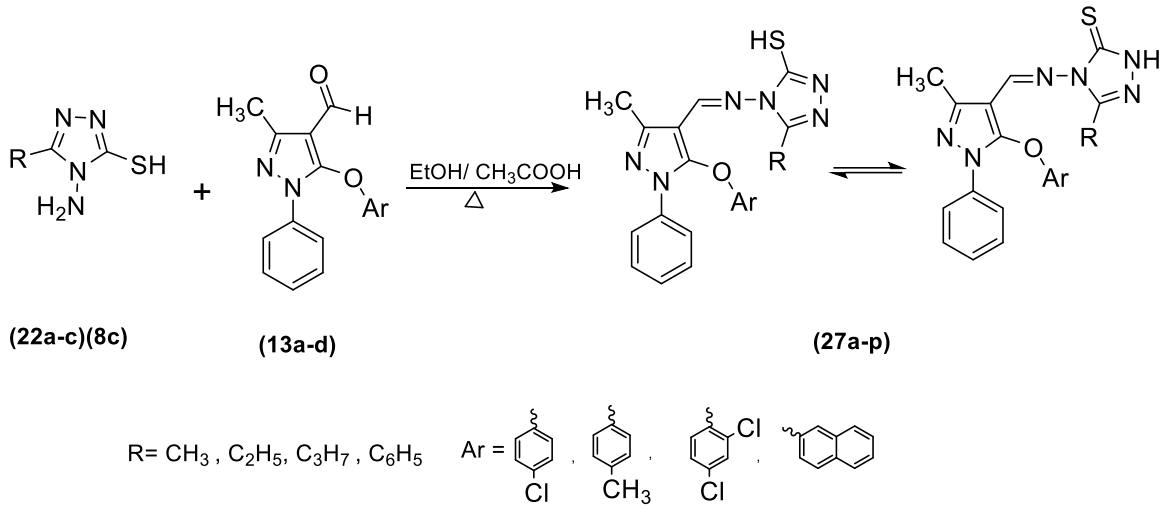
SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDY OF SCHIFF BASES OF 5- SUBSTITUTED PYRAZOLE ALDEHYDE WITH SOME 1,2,4-TRIAZOLE DERIVATIVES

The schematic route for the synthesis of 4-((5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)amino)-5-alkyl/aryl-4H-1,2,4-triazole-3-thiol **(27a-p)** is as shown in **(Scheme 5.1).** The substituted 3-alkyl-4-amino-5-mercapto-1,2,4-triazole **(22a-c),** was synthesized by reacting different substituted acid with thicarbohydrazide, is outlined in **chapter 4 .**

The synthetic route followed for the synthesis of 3-phenyl-4-amino-5-mercapto-1,2,4-triazole **(8c)** and 5-aryloxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde **(13a-d)** is outlined in **chapter 2 .**

Acid catalyzed condensation of 5-aryloxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde **(13a-d)** with 3-alkyl/phenyl-4-amino-5-mercapto-1,2,4-triazole **(22a-c) (8c)** in the presence of acetic acid to gave corresponding pyrazole tethered with 1,2,4-triazole Schiff base derivatives **(27a-p).**

Structure of all newly synthesized compounds were supported by analytical and spectral data. The new compounds were also screened for their antioxidant and antimicrobial activities.



(scheme 5.1)

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2. Synthesis and Biological activity of some new N-bridged heterocycles of piperonal-based triazolo-thiadiazoles, M. Abdul Rahiman , N. Manju , **Sharath C. Lakshmegowda**, Vasanth A. Gangadharappa, *Indian Journal of Heterocyclic Chemistry*., 30, 615-619 (2020)

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1. Synthesis, characterization and pharmacological, study of pyrazole carrying -3-substituted-[1,2,4]triazolo [3,4-b] [1,3,4] thiadiazoles, **Sharath C. L** and Balakrishna Kalluraya, International Conference on Recent advancements in chemistry held at Field Marshal K.M. Cariappa college , Madikeri, during 23rd November 2022.
2. Synthesis, characterization and pharmacological study of Pyrazole Carrying some novel 1,3,4-oxadiazole, **Sharath C. L** and Balakrishna Kalluraya, International Conference on Functional Materials for Advanced Technologies held at Central University of Kerala , during 2-4 January 2023.
3. Synthesis, characterization and Biological study of Schiff bases of 5- substituted pyrazole aldehyde with some 1,2,4-triazole derivatives, **Sharath C. L** and Balakrishna Kalluraya, National Conference on Recent Developments in Chemical Sciences held at Sahyadri Science College , Shivamoga, during 20th and 21st February 2023.

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